ORIGINAL ARTICLE

C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia

Ravi Savarirayan, M.B., B.S., M.D., Melita Irving, M.B., B.S., M.D., Carlos A. Bacino, M.D., Bret Bostwick, M.D., Joel Charrow, M.D., Valerie Cormier-Daire, M.D., Ph.D., Kim-Hanh Le Quan Sang, Ph.D., Patricia Dickson, M.D., Paul Harmatz, M.D., John Phillips, M.D., Natalie Owen, M.S.N., Anu Cherukuri, Ph.D., Kala Jayaram, M.D., George S. Jeha, M.D., Kevin Larimore, Ph.D., Ming-Liang Chan, Ph.D., Alice Huntsman Labed, Ph.D., Jonathan Day, M.B., B.S., Ph.D., and Julie Hoover-Fong, M.D., Ph.D.

ABSTRACT

BACKGROUND

Achondroplasia is a genetic disorder that inhibits endochondral ossification, resulting in disproportionate short stature and clinically significant medical complications. Vosoritide is a biologic analogue of C-type natriuretic peptide, a potent stimulator of endochondral ossification.

METHODS

In a multinational, phase 2, dose-finding study and extension study, we evaluated the safety and side-effect profile of vosoritide in children (5 to 14 years of age) with achondroplasia. A total of 35 children were enrolled in four sequential cohorts to receive vosoritide at a once-daily subcutaneous dose of 2.5 μg per kilogram of body weight (8 patients in cohort 1), 7.5 μg per kilogram (8 patients in cohort 2), 15.0 μg per kilogram (10 patients in cohort 3), or 30.0 μg per kilogram (9 patients in cohort 4). After 6 months, the dose in cohort 1 was increased to 7.5 μg per kilogram and then to 15.0 μg per kilogram, and in cohort 2, the dose was increased to 15.0 μg per kilogram; the patients in cohorts 3 and 4 continued to receive their initial doses. At the time of data cutoff, the 24-month dose-finding study had been completed, and 30 patients had been enrolled in an ongoing long-term extension study; the median duration of follow-up across both studies was 42 months.

RESULTS

During the treatment periods in the dose-finding and extension studies, adverse events occurred in 35 of 35 patients (100%), and serious adverse events occurred in 4 of 35 patients (11%). Therapy was discontinued in 6 patients (in 1 because of an adverse event). During the first 6 months of treatment, a dose-dependent increase in the annualized growth velocity was observed with vosoritide up to a dose of 15.0 μg per kilogram, and a sustained increase in the annualized growth velocity was observed at doses of 15.0 and 30.0 μg per kilogram for up to 42 months.

CONCLUSIONS

In children with achondroplasia, once-daily subcutaneous administration of vosoritide was associated with a side-effect profile that appeared generally mild. Treatment resulted in a sustained increase in the annualized growth velocity for up to 42 months. (Funded by BioMarin Pharmaceutical; ClinicalTrials.gov numbers, NCT01603095, NCT02055157, and NCT02724228.)

From Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Parkville, VIC, Australia (R.S.); Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London (M.I.); Baylor College of Medicine, Houston (C.A.B., B.B.); Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago (J.C.); the Medical Genetics Department, Université Paris Descartes–Sorbonne Paris Cité, INSERM Unité Mixte de Recherche 1163, Institute Imagine, Assistance Publique–Hôpitaux de Paris, Hôpital Necker–Enfants Malades, Paris (V.C.-D., K.-H.L.Q.S.); Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance (P.D.), University of California, San Francisco, Benioff Children's Hospital Oakland, Oakland (P.H.), and BioMarin Pharmaceutical, Novato (A.C., K.J., G.S.J., K.L., M.L.C.) — all in California; Vanderbilt University Medical Center, Nashville (J.P., N.O.); BioMarin, London (A.H.L., J.D.); and Johns Hopkins University School of Medicine, Baltimore (J.H.-F.). Address reprint requests to Dr. Savarirayan at Murdoch Children's Research Institute, Royal Children's Hospital, 50 Flemington Rd., Parkville, VIC 3052, Australia, or at ravi.savarirayan@vcgs.org.au.

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Achondroplasia is the most common form of disproportionate short stature, with a prevalence of 1 in 25,000 live births.[1-5] The condition is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*) that constitutively activates the mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase pathway in chondrocytes, which inhibits endochondral ossification.[6] The hallmark clinical features are short stature with rhizomelic limb-shortening and macrocephaly. Medical complications include hydrocephalus, hypotonia, back and leg pain, conductive hearing loss, and speech delay. Relative tonsillar hypertrophy may result in obstructive sleep apnea and respiratory insufficiency. Foramen magnum stenosis and cervicomedullary compression may result in central apnea, leading to an increased risk of sudden death in infancy.[7-9] Achondroplasia is associated with a condition-specific profile of developmental milestones, functional limitations affecting quality of life, and chronic pain, all of which lead to psychosocial challenges.[8,10-13] Mortality is increased from birth to 4 years of age and in the fourth and fifth decades of life.[14]

No pharmacologic therapies have been approved for achondroplasia, except for growth hormone, which is available for this indication in Japan.[15] Increases in height in children with achondroplasia who are treated with growth hormone occur mainly during the first 2 years of therapy.[16] In a long-term study with a mean follow-up of 10 years, growth hormone therapy in patients with achondroplasia resulted in an increase in final height by a standard deviation of 0.60 (an addition of 3.5 cm) in male patients and by standard deviation of 0.51 (an addition of 2.8 cm) in female patients.[17] The effects of growth hormone on disproportionality are unknown, as are the long-term complications of such therapy.[16-18] Limb-lengthening surgery improves height but does not prevent associated medical complications; in addition, the surgery is controversial because of its invasiveness and high rate of complications.[19]

C-type natriuretic peptide, encoded by *NPPC*, and its receptor, natriuretic peptide receptor 2 (NPR2), are potent stimulators of endochondral ossification.[20] Reduced *Nppc* or *Npr2* expression, or lack thereof, in mice results in severe dwarfism due to impaired endochondral ossification.[21,22] Conversely, overexpression of *Nppc* in mice[23] and of *NPPC* in models of human disease[24-26] is characterized by overproduction of endogenous C-type natriuretic peptide[22,27] resulting in sustained skeletal overgrowth. Continuous intravenous infusion of exogenous C-type natriuretic peptide[28] restores the impaired bone growth observed in mice with achondroplasia and increase long-bone growth in wild-type monkeys by inhibiting the *FGFR3*-mediated MAPK signaling pathway,[29] findings that support the potential for C-type natriuretic peptide–based therapy for achondroplasia.

Vosoritide is a recombinant C-type natriuretic peptide analogue that was developed to have a longer half-life than its endogenous form in order to prolong pharmacologic activity.[30] Once-daily subcutaneous administration of vosoritide promotes long-bone growth in juvenile, skeletally normal mice and monkeys and corrects the dwarfism phenotype in mice with achondroplasia.[29] On the basis of promising preclinical findings, the current phase 2 dose-finding study and the still-ongoing extension study were conducted to evaluate the use of vosoritide in children with achondroplasia.

METHODS

STUDY DESIGN AND OVERSIGHT

This phase 2, open-label, sequential-cohort, dose-finding study (Study 202, ClinicalTrials.gov number, NCT02055157) was conducted from January 2014 through October 2017 at nine study sites (six in the United States and one each in Australia, France, and the United Kingdom). Eligible children were 5 to 14 years of age at screening, had achondroplasia confirmed by genetic testing, and had completed at least 6 months of a run-in observational growth study (Study 901, NCT01603095) to establish their baseline annualized growth velocity. (Additional details of Study 901 are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Children with fused growth plates were excluded.

Study 202 included a 6-month dose-finding phase followed by an 18-month period during which patients either received an escalated dose or continued to receive their initial dose (Fig. S1

in the Supplementary Appendix). During the initial 6 months, patients were treated in four sequential cohorts with a once-daily subcutaneous dose of 2.5 μg per kilogram of body weight (cohort 1), 7.5 μg per kilogram (cohort 2), 15.0 μg per kilogram (cohort 3), or 30.0 μg per kilogram (cohort 4). On the basis of emerging safety and efficacy data, after 6 months, the dose was increased to 7.5 μg per kilogram and then to 15.0 μg per kilogram in cohort 1 and to 15.0 μg per kilogram in cohort 2; patients in cohort 3 and cohort 4 continued to receive their initial doses (Table S1 in the Supplementary Appendix). The children who completed the 24-month dose-finding study were eligible to enroll in an ongoing long-term extension study in which they continued to receive their preassigned dose of either 15.0 μg per kilogram or 30.0 μg per kilogram (Study 205, NCT02724228). The long-term extension study began before it was registered at ClinicalTrials.gov because of an administrative issue. A total of 2 of 30 patients were enrolled before registration. Data through July 11, 2018, are included in the current report, representing a median duration of follow-up of 42 months (range, 0.3 to 52.0).

Trained caregivers administered vosoritide to patients at their homes. Written informed consent from a parent or legal guardian of each patient was obtained, and assent was obtained from the patient, if appropriate. Studies were performed in accordance with the provisions of the Declaration of Helsinki. The study protocols were approved by the relevant ethics boards and are available at NEJM.org.

The sponsor, BioMarin Pharmaceutical, designed and funded the studies, analyzed the data, and provided the trial drug. A medical writer paid by the sponsor, whose work was reviewed by the authors, assisted with manuscript preparation. All the authors vouch for the accuracy and completeness of the data, for the adherence of the studies to the protocols, and for the reporting of adverse events.

Outcomes

The primary objectives were to evaluate the safety and side-effect profile of a once-daily subcutaneous dose of vosoritide and to determine the dose to further investigate in phase 3 studies. Safety was evaluated according to the incidence of adverse events and serious adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0), laboratory test results, vital signs, findings from physical examination and clinical hip assessment, electrocardiographic and echocardiographic results, and detection of an antibody response against vosoritide to characterize any effect on safety, exposure, and efficacy (see the Supplementary Appendix). Imaging assessments yielded measurements of the spine and long bones of the arms and legs, along with data regarding growth plate, bone age, and bone mineral density. A data and safety monitoring committee reviewed safety data every 6 months.

Secondary objectives were to evaluate the effects of vosoritide with respect to the change from baseline in annualized growth velocity (centimeters per year), height z scores, and body-segment proportionality. Vosoritide was also evaluated with respect to its pharmacokinetic profile (see the Supplementary Appendix) and biomarkers of drug activity (urinary cyclic guanosine monophosphate [cGMP]) and endochondral ossification (serum collagen X marker [CXM], a degradation fragment of type X collagen).[31] The baseline concentrations of urinary cGMP were established at each trial visit before the vosoritide dose was administered, and the baseline concentration of CXM was established once on day 1 of treatment before the first dose was administered.

Statistical Analysis

All the patients were included in the safety and efficacy analyses. The data obtained from the patients while they were receiving treatment were compared with the pretreatment data collected during the observational run-in study.

Data regarding the annualized growth velocity, which were based on measurements of standing height taken every 3 months, were summarized with the use of descriptive statistics, with the annualized growth velocity during the last 6 months of the run-in study serving as the baseline. Standing height was converted to a z score that was appropriate for sex and age according to a comparison with the reference standards of the Centers for Disease Control and Prevention[32]; higher scores reflect improvement. The 95% confidence intervals of the changes from baseline in annualized growth velocity, z scores, and ratio

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1 (2.5 μg/kg) (N=8)	Cohort 2 (7.5 μg/kg) (N=8)	Cohort 3 (15.0 μg/kg) (N=10)	Cohort 4 (30.0 μg/kg) (N=9)	All Cohorts (N=35)
Age at screening — yr					
Mean	7.3±1.6	8.3±2.2	8.0±1.6	6.9±1.2	7.6±1.7
Median	7.0	9.5	8.0	7.0	7.0
Range	5–10	5–10	6–11	5–8	5–11
Age group at screening — no. (%)					
5 to <8 yr	6 (75)	3 (38)	4 (40)	5 (56)	18 (51)
8 to <10 yr	1 (12)	1 (12)	4 (40)	4 (44)	10 (29)
10 to ≤14 yr	1 (12)	4 (50)	2 (20)	0	7 (20)
Sex — no. (%)					
Female	5 (62)	3 (38)	6 (60)	5 (56)	19 (54)
Male	3 (38)	5 (62)	4 (40)	4 (44)	16 (46)
Ethnic group — no. (%)†					
Not Hispanic or Latino	8 (100)	8 (100)	9 (90)	7 (78)	32 (91)
Hispanic or Latino	0	0	1 (10)	1 (11)	2 (6)
Not reported	0	0	0	1 (11)	1 (3)
Race — no. (%)†					
White	7 (88)	6 (75)	5 (50)	6 (67)	24 (69)
Asian	0	1 (12)	3 (30)	3 (33)	7 (20)
Black	1 (12)	0	1 (10)	0	2 (6)
Other	0	1 (12)	1 (10)	0	2 (6)
Tanner stage 1 — no./total no. (%)‡					
Pubic hair development§	7/7 (100)	8/8 (100)	10/10 (100)	9/9 (100)	34/34 (100)
Breast development¶	5/5 (100)	3/3 (100)	6/6 (100)	5/5 (100)	19/19 (100)
Genital development‖	2/2 (100)	5/5 (100)	4/4 (100)	4/4 (100)	15/15 (100)

* Plus–minus values are means ±SD. There were no significant between-group differences in the baseline characteristics listed in the table. Percentages may not total to 100 because of rounding. Vosoritide was administered subcutaneously in once-daily doses. Cohort 1 received an initial dose of vosoritide of 2.5 μg per kilogram of body weight; cohort 2, a dose of 7.5 μg per kilogram; cohort 3, a dose of 15.0 μg per kilogram; and cohort 4, a dose of 30.0 μg per kilogram.
† Race and ethnic group were determined by the investigators through specific questioning of parents or guardians of the participating children at enrollment.
‡ Tanner stages range from 1 to 5, with higher stages indicating more advanced pubertal development.
§ Pubic hair development was assessed in all children, except for one boy in cohort 1.
¶ Breast development was assessed in all girls.
‖ Genital development was assessed in all boys, except for one in cohort 1.

of the upper-body segment to the lower-body segment were based on one-sample Student's t-tests with the assumption of normality and are considered to be descriptive; no adjustments were made for multiple comparisons.

RESULTS

PATIENTS

A total of 35 children (19 girls and 16 boys) with a mean (±SD) age of 7.6±1.7 years (range, 5 to 11) were enrolled in the four sequential cohorts (Table 1). As of July 11, 2018, the dose-finding study was completed, and 30 patients had been enrolled in the long-term extension study. During the first 6 months of the dose-finding study, 1 patient in cohort 1 withdrew consent, and 1 patient in cohort 2 discontinued treatment because of fear of needles and injections. One patient in cohort 4 was withdrawn after receiving a diagnosis of grade 1, intermittent Wolff–Parkinson–White syndrome, which was identified on routine

electrocardiography; this patient had no associated clinical symptoms and remained asymptomatic with no episodes of supraventricular tachycardia for the duration of participation in the study. During the last 18 months of the dose-finding study, 1 patient in cohort 1 discontinued treatment because of fear of needles and injections, and 1 patient in cohort 2 discontinued treatment because of closure of growth plates. Among the 30 patients who were enrolled in the long-term extension study, 1 withdrew from the study to undergo limb-lengthening surgery.

Forty-two months of efficacy data were available for 6 patients in cohort 1, 6 patients in cohort 2, and 10 patients in cohort 3; 30 months of efficacy data were available for 8 patients in cohort 4. Up to 52 months of safety data were available for 12 patients in cohorts 1 and 2, up to 45 months in cohort 3, and up to 34 months in cohort 4.

ADVERSE EVENTS AND SAFETY

During the treatment periods in the dose-finding and extension studies, adverse events occurred in 35 of 35 patients (100%). Common adverse events that occurred during the treatment period are listed in Table 2, and all adverse events are listed in Table S2 in the Supplementary Appendix. All injection-site reactions were mild (grade 1) and transient. Antidrug antibody responses were detected in 14 of 35 patients (40%) at one or more assessment visits. Among the 14 patients in whom an antidrug antibody response had developed, the serum total antibody titers were transient in 7, with the titers declining to undetectable levels, but were sustained in the other 7 patients at the end of the dose-finding study. Neutralizing antibodies were detected in 2 patients at a single visit. No association was observed between antidrug antibody positivity and frequency or severity of hypersensitivity or injection-site reactions.

Blood pressure and pulse rate were monitored frequently after the initial dose was administered. All reductions in blood pressure from test to test were reported as nonserious and transient and resolved without medical intervention; none resulted in interruption or discontinuation of the study-drug regimen. All changes in blood pressure or pulse rate were asymptomatic, except in one patient in cohort 1 who had a single symptomatic hypotensive event on day 281 of the extension study, which was transient and resolved without medical intervention.

During the treatment periods in the dose-finding and extension studies, serious adverse events occurred in 4 of 35 patients (11%) and included grade 3 obstructive sleep apnea, grade 1 tonsillar hypertrophy, grade 3 thyroglossal cyst, and grade 3 syrinx. No deaths occurred. No adverse events related to disproportionate skeletal growth or clinically significant adverse cardiovascular effects were observed. In addition, there were no reports of grade 3 or higher hypersensitivity reactions, and no patients reported adverse events that were consistent with the criteria for anaphylaxis of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network.

ANNUALIZED GROWTH VELOCITY

During the first 6 months of treatment, a dose-dependent increase in the annualized growth velocity was observed in the patients who received vosoritide at a dose of up to 15 μg per kilogram (Fig. 1A, and Table S3 in the Supplementary Appendix). At 6 months, increases in annualized growth velocity from baseline were observed in cohort 2 (1.28 cm per year; 95% confidence interval [CI], 0.07 to 2.48), in cohort 3 (2.01 cm per year; 95% CI, 0.58 to 3.44), and in cohort 4 (2.08 cm per year; 95% CI, 0.30 to 3.87) but not in cohort 1 (−0.37 cm per year; 95% CI, −1.84 to 1.10). The changes in annualized growth velocity from baseline in cohorts 3 and 4 were similar, despite a greater-than-dose-proportional increase in plasma exposure to vosoritide (Table S4 in the Supplementary Appendix).

During the extension study, continued administration of vosoritide resulted in a sustained increase in annualized growth velocity for up to 42 months (the time of data cutoff) (Fig. 1B, and Table S5 in the Supplementary Appendix). Bone age progressed normally in all cohorts through 36 months (Table S6 in the Supplementary Appendix).

The annualized growth velocity increased from baseline in all cohorts during each 12-month interval by 1.10 to 2.34 cm per year for up to 42 months (Table S7 in the Supplementary Appendix). Among the patients who received the 15.0-μg-per-kilogram dose, the mean annualized growth velocity was 5.51 cm per year, as calculated between 30 and 42 months. This change represented an annual increase of 1.46 cm (95% CI, −0.15 to 3.07) from baseline. Among the patients who received the 30.0-μg-per-kilogram

Table 2. Incidence of Common Adverse Events That Occurred during the Treatment Periods in the Dose-Finding and Extension Studies.*

Adverse Event	Vosoritide Dose Level†				Overall Study Population (N=35)
	2.5 μg/kg (N=8)	7.5 μg/kg (N=15)	15.0 μg/kg (N=22)	30.0 μg/kg (N=9)	
	number of patients with event (percent)				
Injection-site erythema	4 (50)	7 (47)	14 (64)	9 (100)	30 (86)
Injection-site reaction	2 (25)	8 (53)	17 (77)	9 (100)	30 (86)
Pyrexia	4 (50)	2 (13)	13 (59)	3 (33)	19 (54)
Cough	4 (50)	2 (13)	10 (45)	4 (44)	17 (49)
Hypotension	4 (50)	5 (33)	7 (32)	2 (22)	16 (46)
Injection-site swelling	4 (50)	2 (13)	8 (36)	2 (22)	16 (46)
Nasopharyngitis	1 (12)	3 (20)	12 (55)	2 (22)	16 (46)
Headache	4 (50)	3 (20)	8 (36)	3 (33)	14 (40)
Nasal congestion	1 (12)	2 (13)	7 (32)	2 (22)	12 (34)
Upper respiratory tract infection	0	1 (7)	10 (45)	2 (22)	12 (34)
Ear pain	2 (25)	3 (20)	6 (27)	2 (22)	11 (31)
Vomiting	2 (25)	2 (13)	6 (27)	3 (33)	11 (31)
Ear infection	1 (12)	4 (27)	7 (32)	2 (22)	10 (29)
Oropharyngeal pain	1 (12)	2 (13)	7 (32)	1 (11)	10 (29)
Otitis media	1 (12)	0	7 (32)	3 (33)	10 (29)
Pain in arms or legs	1 (12)	0	5 (23)	4 (44)	10 (29)
Injection-site urticaria	1 (12)	2 (13)	3 (14)	4 (44)	9 (26)
Arthropod bite	1 (12)	2 (13)	5 (23)	1 (11)	8 (23)
Fall	2 (25)	1 (7)	4 (18)	2 (22)	8 (23)
Viral infection	0	0	7 (32)	1 (11)	8 (23)
Upper abdominal pain	1 (12)	1 (7)	4 (18)	1 (11)	7 (20)
Rhinorrhea	2 (25)	1 (7)	3 (14)	1 (11)	7 (20)

* Adverse events with an incidence of at least 20% in the overall study population are shown. Patients who had more than one adverse event within a given preferred term during the treatment period were counted once within that preferred term. Adverse events were coded with the use of preferred terms from the *Medical Dictionary for Regulatory Activities*, version 19.1.

† Patients who received an escalation in dose are summarized in more than one dose column.

dose, the mean annualized growth velocity was 5.60 cm per year, as calculated between 18 and 30 months. This change represented an annual increase of 1.10 cm (95% CI, −0.27 to 2.48) from baseline (Table S7 in the Supplementary Appendix).

z Scores for Height

Dose-dependent increases in z scores for height were observed in the patients who received a dose of up to 15.0 μg per kilogram for 6 months; those who received a dose of 30.0 μg per kilogram had an increase similar to that with the 15.0-μg-per-kilogram dose. Vosoritide resulted in a sustained increase in z scores for height for up to 42 months; the mean increase from baseline to 42 months was 0.98±0.99 in cohort 1, 0.49±0.49 in cohort 2, and 1.03±0.57 in cohort 3; the mean increase from baseline to 30 months was 1.06±0.30 in cohort 4 (Table S8 in the Sup-

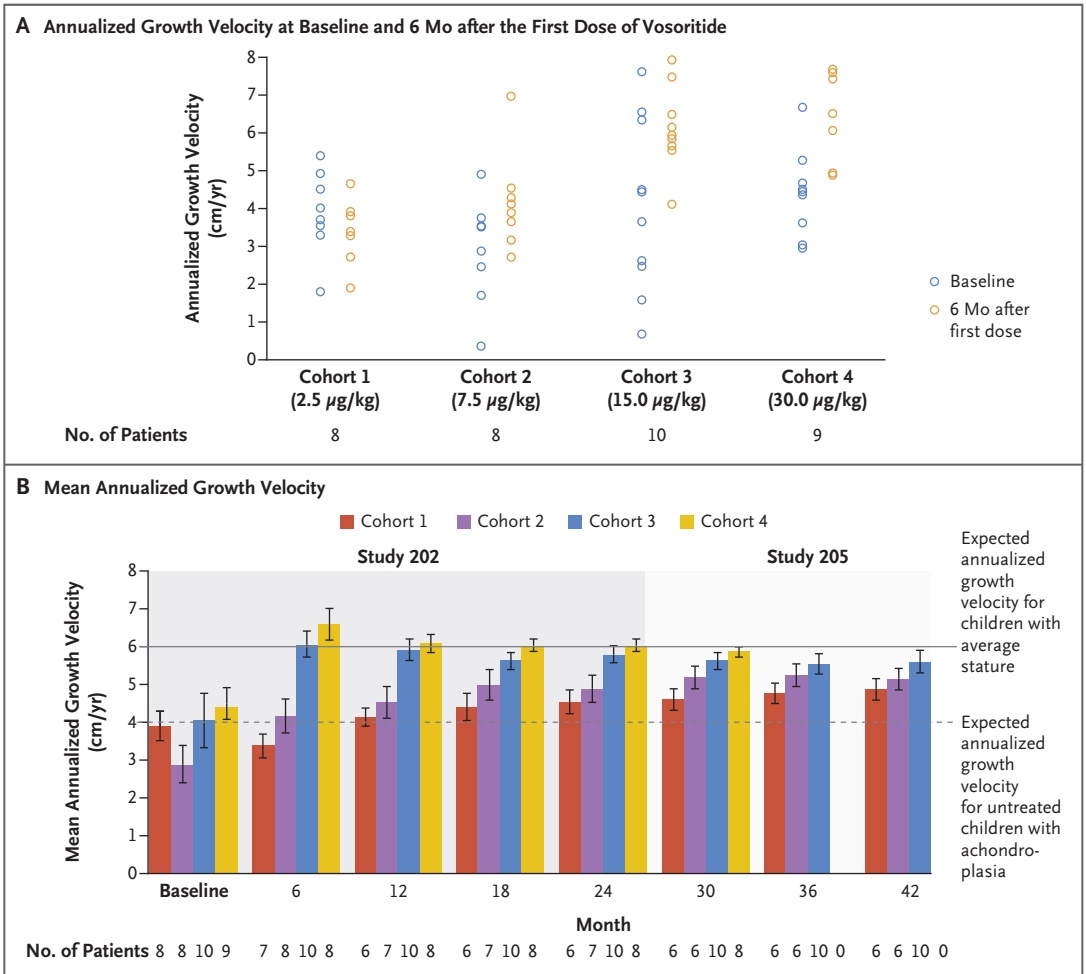

Figure 1. Annualized Growth Velocity at Baseline and during the Treatment Period.

Panel A shows a vertical scatter plot of the annualized growth velocity at baseline and at 6 months after the first dose of vosoritide according to cohort. Patients with data on annualized growth velocity at both baseline (blue circles) and 6 months after the first dose (orange circles) were included. The annualized growth velocity at baseline was established with the use of data from the last 6 months of the observational run-in study before the screening visit. The annualized growth velocity at the 6-month visit was based on standing height and was calculated as follows: (height at the 6-month visit − height at the baseline visit)/interval length in days × 365.25. Panel B shows the mean annualized growth velocity summarized up to 42 months in cohorts 1, 2, and 3 and up to 30 months in cohort 4. After 6 months of treatment with the assigned dose of vosoritide, the dose in cohort 1 was increased to 7.5 μg per kilogram and then to 15.0 μg per kilogram, and in cohort 2, the dose was increased to 15.0 μg per kilogram; cohorts 3 and 4 continued to receive their initial doses. Every 6 months, the annualized growth velocity was recalculated from baseline. I bars indicate standard errors. The dashed horizontal line represents the expected annualized growth velocity for untreated children with achondroplasia.[32] The solid horizontal line represents the expected annualized growth velocity for children with average stature over the corresponding age interval of the children reported in studies 202 and 205.[32]

plementary Appendix). After the baseline observation period had been completed and treatment with vosoritide initiated (Fig. 2), the slopes of the regression lines for the z score were positive (indicating improvement) in all cohorts.

BODY PROPORTION

Proportional growth between the upper-body and lower-body segments was observed from baseline to month 42 in cohorts 1, 2, and 3 and from baseline to 30 months in cohort 4. There were

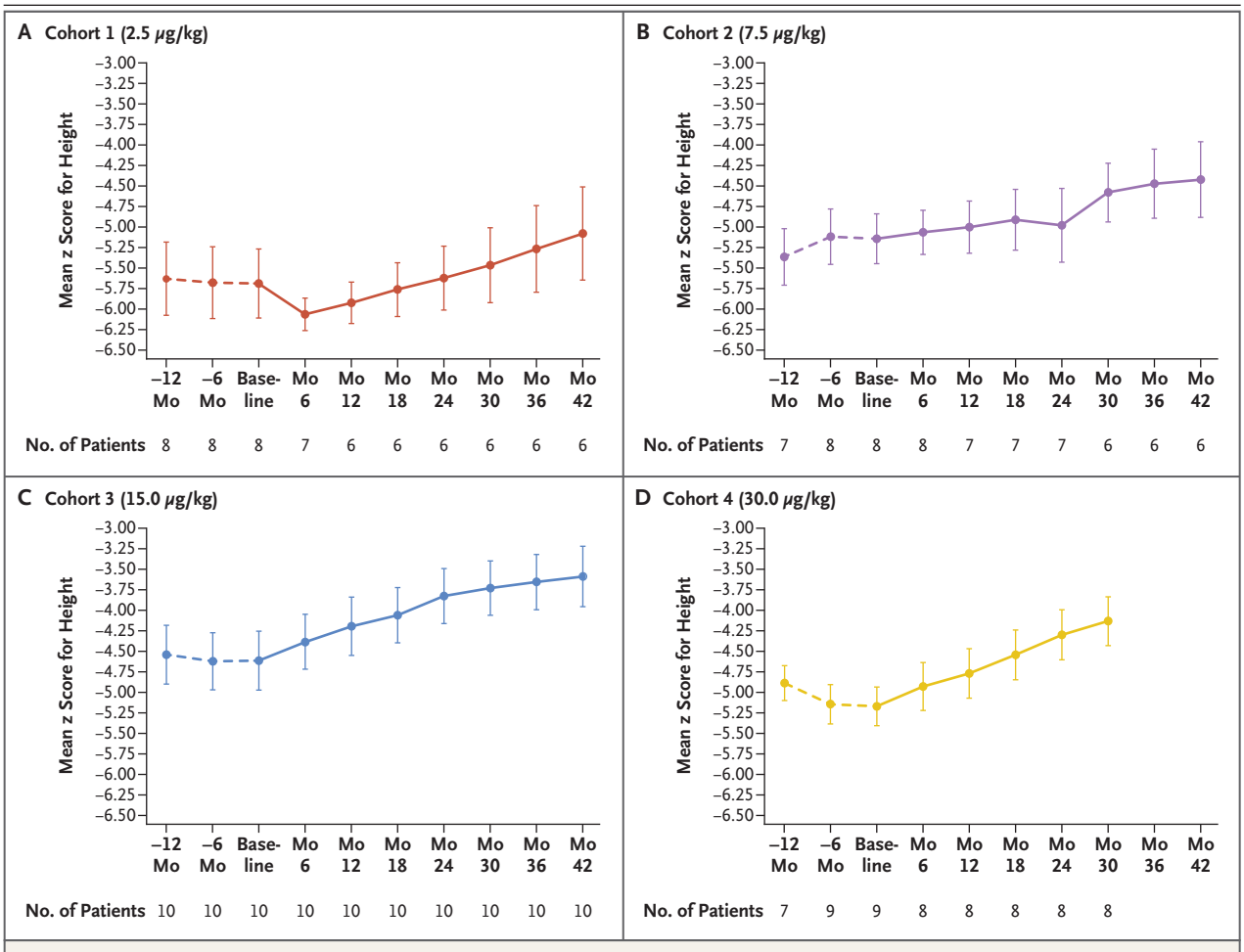

Figure 2. Mean z Scores for Height at Baseline and during the Treatment Period.

The figure shows the mean z scores for height during the last 12 months of the observational growth study and during the treatment period in cohorts 1, 2, and 3 through 42 months (Panels A to C) and in cohort 4 through 30 months (Panel D). After 6 months of treatment with the assigned dose of vosoritide, the dose in cohort 1 was increased to 7.5 μg per kilogram and then to 15.0 μg per kilogram, and in cohort 2, the dose was increased to 15.0 μg per kilogram; cohorts 3 and 4 continued to receive their initial doses. The z scores were derived from age- and sex-specific reference data from the Centers for Disease Control and Prevention[32]; higher scores reflect improvement. I bars indicate standard errors. After the baseline observation period had been completed and treatment with vosoritide initiated, the slopes of the regression lines for the z score were positive (indicating improvement) in all cohorts.

no clinically relevant changes in the body-segment ratio (Table S9 in the Supplementary Appendix).

SENSITIVITY ANALYSES

Findings from sensitivity analyses of annualized growth velocity and z score for height, in which we used multiple imputation to account for missing assessments of patients who discontinued treatment before 42 months, were consistent with the results of the efficacy analyses reported in the dose-finding and extension studies. Additional details are provided in Tables S10 through S12 in the Supplementary Appendix.

BIOMARKERS

Dose-dependent increases in urinary cGMP and serum CXM concentrations were observed during the initial 6 months of treatment in all four cohorts and remained elevated from baseline through 24 months (Fig. 3). These findings suggests that the pharmacologic activity of vosoritide is sustained over the course of treatment, with the

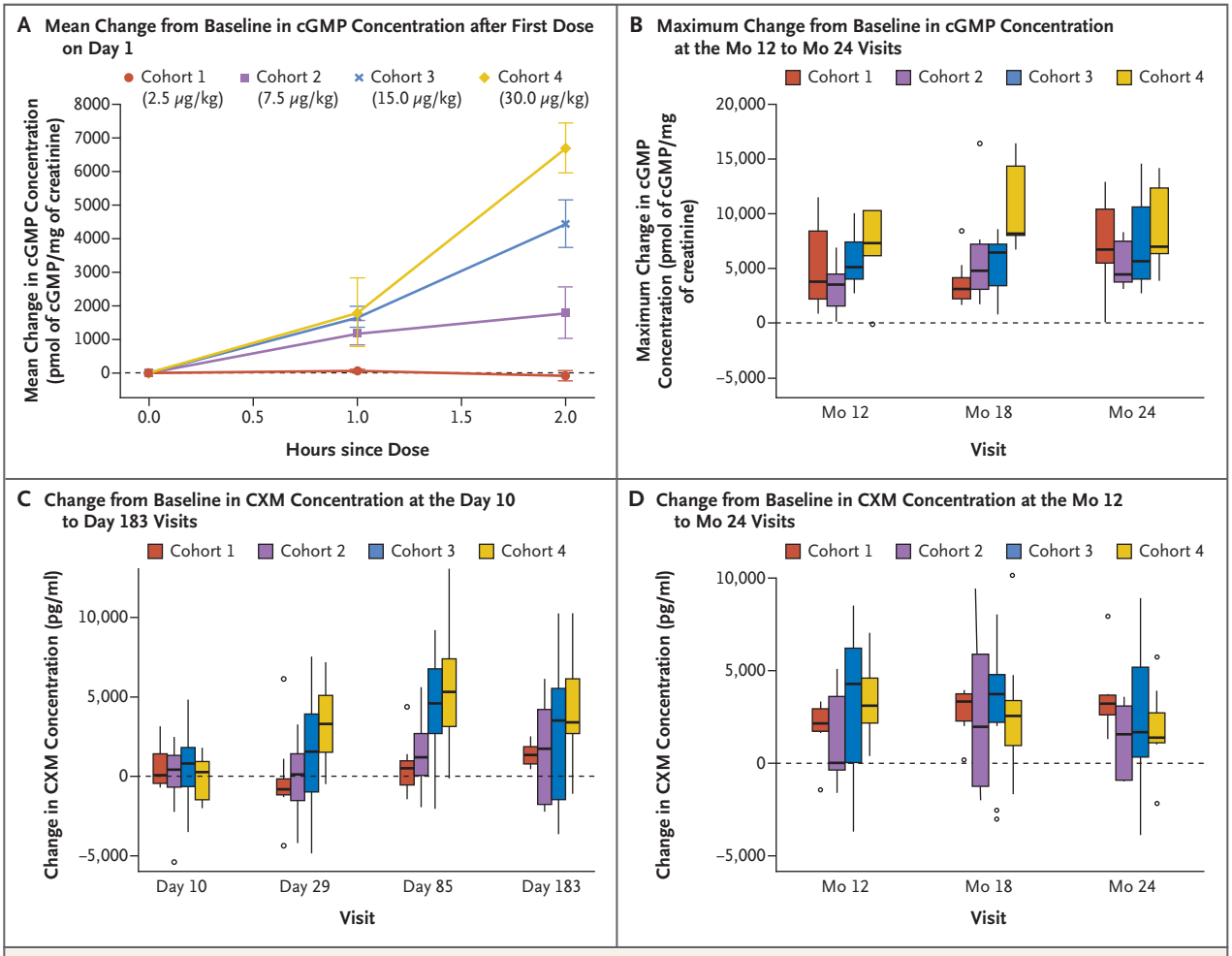

Figure 3. Change from Baseline in Serum Biomarker Concentrations (cGMP and CXM) with Vosoritide.

The baseline concentrations of urinary cyclic guanosine monophosphate (cGMP), measured as picomoles of cGMP per milligram of creatinine, were established at each trial visit before the vosoritide dose was administered, and the baseline concentration of serum collagen X marker (CXM), a degradation fragment of type X collagen, was established once on day 1 of treatment before the first dose was administered. Panel A shows the dose-dependent increases from baseline in the urinary cGMP concentration at 1 and 2 hours after the first dose of vosoritide in each cohort on day 1 of treatment. After 6 months of treatment with the assigned dose of vosoritide, the dose in cohort 1 was increased to 7.5 μg per kilogram and then to 15.0 μg per kilogram, and the dose in cohort 2 was increased to 15.0 μg per kilogram; the dose-dependent increases from baseline in urinary cGMP concentration were sustained for up to 24 months of treatment. Panel B shows the distribution of the maximum change from baseline in the urinary cGMP concentration in each cohort at the month 12 to month 24 visits. At each visit, the cGMP concentration was determined in each patient before the dose was administered and at several time points after; the maximum change was the highest value among the postdose measurements relative to the predose measurement. Panel C shows the dose-dependent increase from baseline in the median serum CXM concentration by day 29 in each cohort, with the concentrations peaking at day 85 to day 183. Panel D shows that the median serum CXM concentration remained elevated relative to baseline in all cohorts from 12 through 24 months. The horizontal bars inside the boxes represent the median, and the boxes represent the interquartile range (IQR), with the lower and upper boundaries of the boxes representing the 25th and 75th percentiles. The ends of the whisker lines represent the minimum and maximum values within 1.5 times the IQR from the lower and upper box boundaries. The open circles represent outliers beyond the range (i.e., 1.5 times the IQR from the lower and upper box boundaries). Panel B was scaled to size, and three high values (37,393.9 pmol of urinary cGMP per milligram of creatinine in cohort 3 at month 18, 27,355.7 pmol of urinary cGMP per milligram of creatinine in cohort 4 at month 12, and 55,939.8 pmol of urinary cGMP per milligram of creatinine in cohort 4 at month 18) are not shown but were included in the analyses.

15.0-μg-per-kilogram and 30.0-μg-per-kilogram doses producing the maximum response.

DISCUSSION

In this dose-finding study and extension study, vosoritide was administered subcutaneously at once-daily doses ranging from 2.5 to 30.0 μg per kilogram for up to 42 months. Findings from the assessment of the safety and side-effect profile of vosoritide (the primary objective) showed that the most common treatment-related adverse events were mild, transient injection-site reactions. Because C-type natriuretic peptide–based therapy can have vascular effects, pulse rate and blood pressure were monitored, and the results indicated that vosoritide was associated with predominantly mild and transient changes in blood pressure. No bone-related adverse events were observed over the entire treatment period.

Administration of vosoritide resulted in a dose-dependent increase in the annualized growth velocity, up to a dose of 15 μg per kilogram, during the first 6 months (with corresponding dose-dependent increases in biomarker concentrations), and the improvement in annualized growth velocity was maintained over 42 months. By 42 months, improvement in the annualized growth velocity was similar among the patients in cohort 1 (initial dose of 2.5 μg per kilogram, with a dose escalation after 6 months to 7.5 μg per kilogram and then to 15.0 μg per kilogram) and cohort 2 (initial dose of 7.5 μg per kilogram, with a dose escalation after 6 months to 15.0 μg per kilogram). The increased annualized growth velocity observed in the patients who received the 15.0-μg-per-kilogram dose or the 30.0-μg-per-kilogram dose for up to 42 months approximated the annualized growth velocity of average-height children of similar age. Height z scores continued to improve over 42 months, in contrast to the decline observed during the pretreatment period.

Proportional growth between the upper-body and lower-body segments was observed, with no clinically relevant change in the body-segment ratio. An ongoing phase 2, randomized, double-blind, placebo-controlled clinical trial (NCT03583697) of vosoritide in infants and younger children (age range, 0 to <60 months) may provide further insights into the effects of treatment on proportionality and other age-specific achondroplasia-related medical complications.

Available data suggest that C-type natriuretic peptide–based therapy may enhance endochondral ossification and improve skeletal growth in children with achondroplasia. C-type natriuretic peptide–based therapy explicitly addresses the underlying pathophysiologic mechanisms of achondroplasia by down-regulating *FGFR3* signaling through the MAPK pathway and counteracting the effects of constitutively active *FGFR3*.[33] In mouse models, *Nppc* overexpression leads to overgrowth of the axial appendicular and craniofacial skeleton and ameliorates the skeletal, craniofacial, and foramen magnum abnormalities of the achondroplasia phenotype.[23,27,28,30]

A transient dose-dependent increase in urinary cGMP concentration, a biomarker of systemic vosoritide pharmacologic activity, from the predose level to at least 2 hours after the dose was administered was observed on day 1; the transient increase after each dose was sustained throughout the dose-finding study — a finding that indicates durable drug activity. A dose-dependent increase in the median serum CXM concentration, a specific biomarker of endochondral ossification, from the pretreatment level was also observed by day 29; the CXM concentration remained elevated through day 183. In all cohorts, the median serum CXM concentrations were similar and remained elevated from month 12 through month 24. This finding indicates that exposure to vosoritide at the 15-μg-per-kilogram dose results in a sustained and maximum response in serum CXM concentration and is consistent with the near-maximum treatment effect observed with regard to annualized growth velocity at this dose. Together, these findings suggest that the greater systemic pharmacologic activity of vosoritide at the 30.0-μg-per-kilogram dose, as indicated by the urinary cGMP concentration, does not appear to result in additional endochondral ossification, as indicated by the serum CXM concentration.

No difference in efficacy or safety could be identified between the once-daily doses of 15.0 and 30.0 μg per kilogram; thus, our findings support the choice of the lower dose for further evaluation in ongoing studies. A phase 3, randomized, double-blind, placebo-controlled trial (NCT03197766) is currently evaluating the efficacy and safety of the 15.0-μg-per-kilogram dose of vosoritide in up to 110 children (age range, 5 to <18 years) with achondroplasia. An open-label phase 3 extension study (NCT03424018)

will further evaluate the efficacy and safety of vosoritide until patients reach final adult height.

Once-daily subcutaneous administration of vosoritide was associated with a side-effect profile that appeared to be generally mild. Treatment resulted in a sustained increase in the annualized growth velocity for up to 42 months.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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